Number 5

Health Technology Assessment

Autologous Peripheral Stem-Cell Transplantation

U.S. Department of Health and Human Services
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Abstract

Autologous peripheral stem-cell transplantation (APSCT) has been extensively applied to support cancer patients who have undergone high-dose chemotherapy (HDCT) and suffer from the effects of otherwise prolonged or irreversible myelosuppression. The APSCT process involves harvesting of autologous progenitor cells from a patient's circulating blood (via leukapheresis), cryopreservation of the cells, and subsequent intravenous infusion for bone marrow hematopoietic reconstitution (HR). Although pluripotent stem cells, capable of multilineage differentiation, cannot be distinguished by morphologic criteria, they can be characterized as being CD34+ cells capable of indefinite self-renewal in situ and long-term self-renewal in cell cultures. Bone marrow and peripheral blood are common sources of autologous progenitor cells. Current techniques to identify and separate CD34+ cells for use in APSCT have resulted in fewer tumor cells being infused than if unseparated peripheral stem cells (PSC) were transplanted, with no differences noted in HR. Chemotherapy- and cytokine-induced mobilization results in increases in progenitor cells, necessitating fewer phereses to harvest sufficient numbers of progenitor cells for engraftment. This assessment addresses the safety, efficacy, and cost-effectiveness of the use of PSC for HR and improving patient outcome, as well as the indications and criteria for patient selection for the use of APSCT. Available information from study panels, research centers, institutions, and government agencies is reviewed; randomized clinical tests (or lack thereof) are discussed; and comparisons are made between APSCT and autologous bone marrow transplantation (ABMT), an accepted therapy in treatment of some malignancies (e.g., leukemia and lymphoma). The author concludes that existing evidence indicates that PSC can provide satisfactory HR, and the rate of HR via PSC does not seem consistently different from that of ABMT. The clinical importance of HR continues to be secondary to the primary issue of the patient benefits of HDCT in terms of antitumor response, palliation, or survival.

Foreword

The Office of Health Technology Assessment (OHTA) evaluates the risks, benefits, and clinical effectiveness of new or unestablished medical technologies. In most instances, assessments address technologies that are being reviewed for purposes of coverage by federally funded health programs.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the *Federal Register* and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps ensure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature.

OHTA analyzed and synthesized data and information received from experts and the scientific literature. The results are reported in this assessment. Each assessment represents a detailed analysis of the risks, clinical effectiveness, and uses of new or unestablished medical technologies. If an assessment has been prepared to form the basis for a coverage decision by a federally financed health care program, it serves as the Public Health Service's recommendation to that program and is disseminated widely.

OHTA is one component of the Agency for Health Care Policy and Research (AHCPR), Public Health Service, Department of Health and Human Services.

Thomas V. Holohan, M.D., FACP
Director
Office of Health Technology Assessment

Clifton R. Gaus, Sc.D.
Administrator
Agency for Health Care Policy and Research

Questions regarding this assessment should be directed to:

Office of Health Technology Assessment
AHCPR
Willco Building, Suite 309
6000 Executive Boulevard
Rockville, MD 20852
Telephone: (301) 594-4023

Contents

Autologous Peripheral Stem-Cell Transplantation

Prepared by: Harry Handelsman, D.O.

Autologous peripheral stem-cell transplantation (APSCT) is a process in which autologous progenitor cells are harvested from a patient's circulating blood via leukapheresis techniques and commonly cryopreserved (with or without enrichment) for subsequent intravenous infusion to effect hematopoietic reconstitution (HR) of the bone marrow (BM) after severe cytopenia associated with high-dose chemotherapy (HDCT) and/or radiotherapy regimens used to treat various malignancies.[1,2] Pluripotent stem cells (capable of multilineage differentiation) cannot be distinguished by morphologic criteria. However, they can be characterized as being CD34+ cells possessing indefinite self-renewal capacity in situ and long-term self-renewal capacity demonstrated in cell cultures.[3-7]

Although the literature commonly treats stem cells as being synonymous with progenitor cells, pluripotent stem cells are in fact the primitive precursors of more committed progenitor cells, which in turn are precursors of all the mature blood cell lineages.[7-9]

Bone marrow transplantation (BMT) associated with HDCT, which has achieved the status of an accepted therapy in the treatment of some malignancies, e.g., leukemia and lymphoma, is also being proposed as a treatment of choice for some selected subsets of patients with other tumors, e.g., breast cancer and multiple myeloma.[1,10] Stem cells are administered as supportive care to circumvent the morbidity and mortality associated with high-dose treatment regimens which are used in attempts to effect a cure or prolonged survival in patients at high risk for treatment failure or recurrent cancer using conventional therapy.[11-13] Both BM and peripheral blood are currently common sources of autologous progenitor cells, and to date, BM has been the primary source.[14-15] In the future, cultured stem cells derived from fetal liver or obtained from umbilical cord blood may provide a reliable source of stem cells as an alternative to autologous cells for transplants.[16-23]

Hematopoietic stem cells usually reside within BM sinusoids.[24] However, smaller numbers (1/10-1/100 of that present in BM) normally circulate in the peripheral blood.[25-30] These can be harvested by multiple leukaphereses (during a 1- to 2-week period) either in an unperturbed (steady) state, during the transient phase of blood count overshoot occurring during recovery from chemotherapy- or radiotherapy-induced myelosuppression, and/or enhanced by mobilization using cytokines (commonly the recombinant growth factors granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage-colony stimulating factor (GM-CSF).[14,27,30-35] This mobilization results in a substantial (albeit transient) rise in the number of circulating progenitor cells; however, the mechanism(s) by which this is accomplished remains poorly understood.[36-39] The use of cytokine mobilization may be problematic because of the possibility of stimulating the proliferation of residual malignant cells, forcing such cells from marrow into the peripheral circulation (comobilization), and inducing differentiation of pluripotent stem cells to more committed progenitor cells.[40]

In a recent report, current techniques to identify and separate CD34+ cells for use in APSCT resulted in fewer tumor cells being infused than if unseparated peripheral stem cells (PSC) were transplanted, with no differences noted in the resultant HR.[41]

Although optimal methods and appropriate timing of harvesting remain uncertain (as do the quantity and quality of the cells), PSC are commonly collected during outpatient leukapheresis using a continuous-flow blood cell separator.[42-44] Approximately 9-14 L of blood are processed over a 2- to 4-hour period. The majority of the blood cells and plasma are returned to the patient, and a final volume of approximately 200 mL is collected and cryopreserved (although occasionally stored unfrozen for short-term use).[45]

The relatively few progenitors seen in peripheral blood require an average of 6-10 pheresis over a period of 5-7 days to obtain sufficient numbers of cells for engraftment.[46,47] Chemotherapy-induced mobilization results in a 10- to 20-fold increase in the number of progenitors, and another 10- to 100-fold increase may be seen after the administration of cytokines.[38,46,48] These increases of progenitor cells (in both percentage and number) in the peripheral blood serve to reduce the

number of phereses required to obtain adequate numbers of cells for successful engraftment to 1-5.[38,41,46,48] However, such yields are not obtainable in heavily pretreated patients.[35,44,49-52] Peripheral stem cells have been commonly measured as colony-forming-unit granulocyte-macrophage progenitor cells (CFU-GM), or CD34+ cells.[53-55] Although the definition of an adequate harvest is uncertain, at least one million purified progenitor cells, 20 x 10^4 CFU-GM, or 2 x 10^7 CD34+ cells/kg body weight or approximately 3-6 x 10^9 mononuclear cells/kg body weight are thought to be potentially adequate for successful transplants in adults[28,41,56,57,58] and 3 x 10^5 cells/kg in children.[27,36,49] A recent report indicated effective HR using unprocessed whole blood after progenitor cell mobilization using cytokines alone.[59]

The primary issues addressed in this assessment (prepared for the Office of Civilian Health and Medical Program of the Uniformed Services) are the safety and effectiveness of PSC for promoting HR and improving patient outcome and the indications and patient selection criteria for the use of APSCT.

Background

The use of autologous bone marrow transplantation (ABMT) has been extensively applied as a technique to support patients after HDCT that would otherwise be associated with unacceptable morbidity and mortality related to infection and bleeding as a consequence of prolonged or irreversible myelosuppression.[46,60] This has occurred without convincing evidence derived from randomized clinical trials (RCTs).[61] The benefits of such support therapies include reduced severity and duration of blood count nadirs, fewer infection and bleeding episodes, reduced requirements for red cell or platelet transfusions, fewer treatment delays, and shorter hospitalizations.[11,62,63] However, despite such support (commonly requiring several weeks of hospitalization), treatment-related mortality is in the range of 5 percent to 25 percent, with the lower rates reported in more recent trials.[39,46,64-69]

The initial rationale for HDCT is based primarily on preclinical chemotherapy trials demonstrating a steep dose-response curve (correlation between chemotherapy dosage and tumor response) and the hypothesis that dose-intensive therapy is associated with increased tumor responses and survival rates.[70,71] Data from some clinical trials and retrospective clinical reviews attempting to confirm the hypothesis surrounding the dose-response curve have been regarded as "promising"[72,73] and "suggestive"[66] but continue to be debated and are not yet proven as conclusive, especially with respect to long-term benefit.[12,38,54,63,65,72-80] It has been suggested that improved durability of responses and survival advantage both appear to be mostly dependent on such prognostic factors as tumor stage and patients' performance status before therapy.[81-84]

A recent metaanalysis of 60 published studies of dose-intensive regimens used in treating small-cell lung cancer failed to demonstrate a positive correlation between dose intensity and outcome.[85] Excepting some lymphomas and leukemias in which randomized trials have been performed, RCTs will continue to be required to determine the extent to which dose intensity determines outcome.[78,86-89]

The use of BM rescue after myelotoxic therapy does not solve the problems of nonhematologic toxicity, which continue to be a dose-limiting barrier to full exploitation of high-dose escalation regimens applied to patients with advanced or refractory malignancies.[1,90-92]

High-dose chemotherapy usually compromises most of the stem cells capable of providing HR, which has been defined as recovery of neutrophils to greater than 500/μL, platelets greater than 20,000/μL, and hematocrit greater than 25 percent.[43] Questions concerning the necessity of stem-cell rescue for achieving permanent hematopoietic recovery have not been completely resolved and will require prospective RCTs.[81,85] Recent reports have documented the feasibility of subablative HDCT regimens with intensive supportive care (including the use of cytokines) without the need of stem-cell transplants and achieved results comparable to outcomes seen with autologous stem-cell transplants.[80,93-97] Cytokines alone have been shown to accelerate neutrophil recovery, but those in current clinical use do not affect platelet recovery.[98] The nature of the stem cells providing long-term hematopoiesis has not been established, and the specific circulating pluripotent stem cell has not been identified and may exist only in the early stages of embryogenesis (although other progenitor cells appear to be able to differentiate into the various blood cell lineages).[1,9,44,99] It is possible that some autochthonous progenitor cells are resistant to the effects of chemotherapy or radiotherapy and are the ultimate source of marrow recovery and long-term

engraftment, whereas transplanted stem cells provide only short-term rescue.[14,26,100,101] Primitive CD34+ stem cells can be separated from more mature stem cells, and their presence and quantitation are useful as a surrogate marker of the progenitor cells responsible for HR.[3,87,99,102,103] The CD34+ cells mobilized after chemotherapy are predominantly myeloid in phenotype and contain few proliferating cells.[104] In some patients, in vitro purging of tumor cells has produced a marked reduction and often a total absence of detectable progenitors without significant loss of HR capability.[105] Currently, in humans, it is usually not possible to identify the origin of the stem cells that engraft.[28,87,106] Such positive identification will probably require chromosomal or genetic marking of transplanted cells.[1,99,106-109]

Hematopoietic reconstitution by cells in the peripheral blood has been amply demonstrated by numerous animal experiments, beginning with Cavins et al in 1964.[110] The presence of hemopoietic progenitor cells in peripheral blood was demonstrated by McCredie et al in 1971.[111] A 1971 report by Richman et al,[33] hypothesizing that the increased number of circulating CFU-GM cells seen after chemotherapy in humans might be a practical source of autologous stem cells used to support patients receiving intensive chemotherapy, was the initial suggestion for trials of PSC as an alternative to BM in the study of HDCT as a means of improving tumor response rates.[33]

The presence of BM metastases was initially thought to inhibit the potential of PSC harvests; however, chemotherapy-induced mobilization was shown to be capable of stimulating the release of stem cells into the peripheral blood even in the face of extensive marrow involvement.[112]

By 1990, it became clear from a number of published studies that PSC were indeed capable of sustained HR in a manner similar to that of BM in patients treated for a variety of malignancies; initially those having lymphoma, myeloma, or other tumors associated with BM metastases or treatment-related marrow hypocellularity.[26,34,35,113-116] In some studies, PSC were added to BM for the purpose of accelerating HR,[30,47,100,117-119] and more recently, satisfactory HR has been achieved using PSC alone.[47,67,114,115]

Although the presence of progenitor cells in the peripheral blood has been amply documented, many of these cells may already be "committed" to specific lineages (and therefore have finite renewal capacity), raising questions concerning sustained long-term engraftment.[14,28,120-122] Early preclinical studies concluded that PSC has limited potential for self-renewal compared with stem cells from BM.[123] However, the fact that long-term engraftment has been observed in humans given PSC suggests that sufficient numbers of pluripotent stem cells are also present in circulating blood.[124,126] It has been suggested that initial engraftment probably derives from committed stem cells, whereas later phases of engraftment derive from pluripotent stem cells, both of which are present in peripheral blood.[36,47 126,127]

Rationale

The basic rationale for APSCT is based on its purported enhanced HR.[27,48,51,100,119,128,129] Proponents of APSCT suggest that the more rapid HR (especially for platelets)[46] and the reduced morbidity, mortality, and requirements for supportive care seen with APSCT is in contrast to the situation associated with prolonged treatment-related myelosuppression often seen with BMT (particularly after pharmacologic purging).[49,54,63,119,130,131] In addition, suggested advantages of APSCT include the avoidance of general or spinal anesthesia, cell harvesting and providing PSC infusions to outpatients, and use when marrow is deemed unsuitable (tumor infiltration, prior treatment, or age)[14,29,32,36,38,44,132-136] or in circumstances in which sequential cycles of HDCT are contemplated.[4,61,67,75,87,137,138]

A recent report indicated that the immuno-suppression seen with HDCT and BMT, sometimes persisting for years, may be shorter and less severe with HDCT and APSCT.[139] The potential advantage of a more rapid immunologic reconstitution of using PSC (possibly related to infusion of T-lymphocytes) has not been fully evaluated, and conflicting evidence exists regarding immune recovery.[31,140]

Proponents also hypothesize that, because some of the failures of HDCT strategies may be related to reinfusion of malignant cells during BMT, better results might be obtained using PSC, which may be less contaminated by malignant cells than BM.[34,131,141-147]

Review of Available Information

The literature search encompassed all journal articles and textbooks (English and non-English) published between 1975 and December 1994 available through

MEDLINE and ancillary search capabilities of the National Library of Medicine. The key words used in the search were "peripheral blood stem-cell transplantation," "hematopoietic stem cells," and "autologous stem-cell rescue." Titles and abstracts from the peer-reviewed literature numbered 447, from which 25 papers were identified for further review using APSCT in 20 or more patients alone or compared with BMT. The search was expanded to include additional references cited in the reviewed articles and textbooks. Additional information was obtained via a *Federal Register* announcement of this assessment;[148] solicitation of information from professional societies, government agencies, and organizations having interest and/or experience with this technology; preprints of papers submitted for publication; and published abstracts.

Autologous peripheral stem-cell transplantation has been proposed as a safe, reliable, and well-tolerated procedure with associated morbidity less than that seen with BMT.[132,149,150] However, the procedures associated with harvesting the cells and their subsequent infusion are not completely benign, albeit with acceptable and manageable toxicity.

The risks and morbidity associated with apheresis have been well described.[150,151] In a report of 215 aphereses in 61 children (age 17 months to 17 years) with various refractory malignancies, three children experienced marked and persistent cytopenia for longer than 1 week, and all patients required reinfusion of the platelet-rich plasma to treat thrombocytopenia.[37] Reversible cyanosis or hypotension developed in two children, and one had an allergic reaction to the red cells used in the priming of the extracorporeal tubing. Eight aphereses were interrupted because of thrombus formation in the catheters.

In a review of the "safety and efficiency" of apheresis in 125 normal donors and 101 patients after interleukin-2 pretreatment or chemotherapy for malignancy, significant anemia and thrombocytopenia (requiring transfusions) were seen in 20 percent of patients but not in the donor.[151] No other serious procedure-related events were noted.

In a study of 27 lymphoma and leukemia patients undergoing a single apheresis, mild bone pain was noted as the only side effect.[49] In another study, nine lymphoma patients underwent a median of 10 aphereses and, excepting transient cytopenias, tolerated the procedure well.[14] Four patients required 0-1 units of red cells, and five others required 4-8 units.

There is a small but definite risk associated with chemotherapy-induced mobilization. In a study of 15 patients with advanced breast cancer undergoing cyclophosphamide mobilization of PSC, 56 percent of patients given a dose of 4 g/m^2 and all patients who received a 7g/m^2 dose of cyclophosphamide required hospitalization for the treatment of febrile neutropenia, and one patient died of sepsis.[91] This issue may be moot in view of the fact that the use of cytokines has largely displaced cytoxic drugs for stem-cell mobilization.[22]

Side effects associated with PSC infusions have been attributed to the cryoprotectant (dimethyl sulfoxide) content of the infusate and its volume of red cells.[2,152,153] These transient and nondisabling effects seen in the majority of patients include hemoglobinuria, chills, fever, nausea, headache, vomiting, and hypertension. Abnormal signs and symptoms seen less frequently include tachypnea, cough, flushing, diarrhea, and elevated serum creatinine and/or bilirubin.

Recent literature has emphasized the reported increase in myelodysplastic syndrome associated with HDCT and autologous stem-cell transplantation.[154] Included in these reports is a study by Miller et al[155] indicating a significantly greater actuarial risk with PSC than if BM was used (31 ± 33 percent, vs. 10.5 ± 12 percent).

The use of APSCT has dramatically increased during the past 5 years, with the majority of procedures performed in patients having lymphomas associated with hypoplastic or tumor-involved marrow, leukemia, or poor-prognosis breast cancer.[156] A report from the European Bone Marrow Transplant Group indicated that 3,399 autologous stem-cell transplants were performed in 1992, of which 644 involved PSC alone and 261 were PSC combined with BM.[157]

In data obtained from the Statistical Center of the North American Autologous Bone Marrow Transplant Registry (which represents approximately one-half of the transplants performed in the United States and Canada), peripheral blood represented the source of stem cells in 15 percent of transplants for breast cancer in 1989, 26 percent in 1992, and 45 percent in 1993 (incomplete 1993 data).[15] The numbers of breast cancer patients receiving stem-cell transplants in those years were 123, 616, and 431, respectively.

There have been no completed prospective RCTs comparing the effectiveness of APSCT in HDCT regimens compared with ABMT or conventional therapy. As of September 1994, the Physician Data Query (PDQ) registry listed 17 currently active protocols involving the use of PSC. Two protocols were phase I, one was phase I/II, 12 were phase II, and the only phase III study was one involving the use of combined BM plus PSC.

The clinical experience published to date, involving APSCT in 20 or more patients, is summarized in Tables 1 and 2.

Discussion

The proposed advantages of APSCT over ABMT relating to the more rapid HR seen with PSC, the avoidance of general or spinal anesthesia, and its application in patients with unsuitable marrow have been suggested in numerous case series, leading a number of investigators to predict that APSCT may soon replace the use of ABMT in studies involving HDCT, especially in patients with a high risk of the marrow graft harboring malignant cells or in circumstances involving sequential HDCT regimens.[22,32,43,82,131,172-179]

Questions concerning the permanence of HR using PSC await longer followup of currently treated patients and further study using chromosomal and genetic markers.

Despite the absence of an RCT directly comparing the use of PSC vs. BM, the recent existing literature and information obtained from BM transplant registries in both the United States and Europe confirm the increased use of APSCT.[15,180]

The heterogeneity of regimens involving scheduling for priming, harvesting, and infusion, plus the use of various cytokines, has as yet not led to agreement as to the optimum use of PSC.[38,42,44,131,169,174,181] This continued lack of standardization presents difficulties in comparing results from different institutions.[182] In addition, the absolute necessity of any stem-cell rescue for therapy-induced myelotoxicity continues to be questioned.[66,93-97,183]

Although PSC harvests appear to contain fewer malignant cells than are seen in BM harvests,[142,145,146] issues surrounding the significance of such stem-cell contamination to the risk of relapse have not been resolved, and in the absence of a clinical trial it is impossible to determine the relative benefit of purged marrow vs. PSC.[57,131,149,184] Recent data suggest that, in patients with solid tumors without evidence of marrow involvement, mobilization regimens result in recruitment of tumor cells into the peripheral blood.[144,185,186] However, the ability to detect small numbers of cancer cells in a stem-cell harvest continues to be poor, and questions concerning the need for purging remain unanswered.[32,66]

There has been a complete lack of uniform reporting of patient selection criteria in all the published reports on the use of stem cells for HR, as well as their impact on response rates or survival. The available data from Table 2 and other reports appear to suggest but do not confirm the hypothesis that patients given PSC transplant experience shorter periods of neutropenia and thrombocytopenia and have reduced treatment-related morbidity (as reflected in the duration of hospitalization) than "comparable" patients receiving BMT.[127,187] Mechanisms responsible for a potentially more rapid HR using PSC have not been elucidated. However, suggested explanations include the fact that approximately 10-fold more cells are infused than are commonly contained in a marrow autograft, and peripheral blood contains more mature ("committed") stem cells that require less time for maturation.[128] Long-term engraftment does not appear to be dependent on the source of the stem cells.[156] Whether long-term engraftment will be sustained over a period of years has yet to be established.[4,22,139,182,188]

Although investigators have commented on the reduced costs associated with APSCT,[62,189,190] the only published data of the relative costs of using PSC vs. BMT appeared as a letter to the editor,[191] a brief comment in one report,[159] one editorial,[179] and one abstract.[192] The letter noted that the major impact of the use of PSC was on posttransplant hospitalization, which was reduced from 26 days using BM in 19 patients to 14 days using PSC in 4 patients (patient selection criteria were not stated). There was also a reduction in the use of antibiotics; blood product support; and pathology, radiology, and microbiology costs. The total cost of using PSC was 25 percent less than the cost of BMT.

The report (from the France Autograft Group) indicated that the shortened hospitalization and reduced need for antibiotic and transfusion support, plus the lack of need for purging resulted in a 50 percent reduction in total cost of transplantation using PSC. The editorial stated that the use of PSC rather

Table 1. Clinical experience involving APSCT

Year	Author	Tumor	No. of patients	Transplant	HR days ANC (0.5 x 10^9/l)	PLT	Days	Median hospital stay (days)
1989	Reiffers[158]	Neuroblastoma leukemia, lymphoma, multiple myeloma	68	PSC	14	50 x 10^9/l	26	NR
1990	Elias[46]	Metastatic breast cancer	12	PSC	14	20 x 10^9/l	12	24
		Solid-tumor	12	PSC + BM	17		16	27
		Metastatic breast cancer	29	BM	21		23	38
1990	Henon[159]	Acute leukemia in remission	52	PSC	15	50 x 10^9/l	27	NR
1990	Iacone[160]	Hematologic malignancies	22	PSC	12	50 x 10^9/l	16	38.5
1990	Takaue[161]	Childhood leukemia and lymphoma	31	PSC	11	50 x 10^9/l	18	NR
1991	Kessinger[162]	Relapsed lymphoma and BM metastases	53	PSC	31	20 x 10^9/l	26	NR
1991	Lopez[144]	Advanced malignancies	10	PSC + BM (purged)	15	50 x 10^9/l	13.5	22
			10	PSC + BM	25		24	20
			6	BM (purged)	20.5		13.5	31
			14	BM	33.5		28	29
1992	Advani1[3]	Lymphomas	16	BM	19	NR		NR
			14	BM + GM-CSF	19			
			13	BM + PSC	15			
			13	BM + PSC + GM - CSF	12			
			4	PSC	15			
			9	PSC + GM-CSF	12			
1992	Brice[163]	Advanced lymphomas	24	PSC	18	50 x 10^9/l	19	NR
1992	Dreyfus[136]	High-risk lymphomas (BM metastases or hypoplasia)	21	PSC	13	NR		NR
1992	Henon[140]	Various malignancies	20	BM	21	50 x 10^9/l	48	28
			20	PSC	15		31	18
1992	Juttner[164]	NR	38	PSC	11	50 x 10^9/l	13.5	16.5
			13	BM	22		32	25
1992	Rowlings[165]	Poor-prognosis malignancies	22	PSC (mobilized)	11	Nadir x 10^9/l	13	NR
			37	CT x 7 g/m^2 PSC CT x 4 g/m^2	9		39	
1992	Takaue[27]	Childhood malignancies	61	PSC	12	50 x 10^9/l	50	NR
1993	Fermand[166]	High-tumor-mass multiple myeloma	63	PSC	15	25 x 10^9/l	16	NR
1993	Kawano[167]	Various malignancies	26	PSC	16	50 x 10^9/l	42	NR
1993	Pettengell[49]	Poor-prognosis leukemia, lymphoma	40	PSC + cytokine	9	20 x 10^9/l	10	13
1993	Schwartz-berg[168]	Advanced malignancies	52	PSC	13	20 x 10^9/l	10	NR
1994	Ayash[169]	Metastatic or locally recurrent breast cancer	20	PSC	7	20 x 10^9/l	6	NR
1994	Bishop[68]	Refractory malignancies	80	PSC (nonmobilized)	26	"Independence"	24	NR
			31	PSC + low-dose cytokine	23		24	
			23	PSC + high-dose cytokine	18		15	
1994	Brice[170]	Malignant lymphomas	37	PSC (nonmobilized)	17	50 x 10^9/l	17	30
			23	PSC mobilized with G-CSF	10	50 x 10^9/l	17	23

Table 1. Clinical experience involving APSCT (continued)

Year	Author	Tumor	No. of patients	Transplant	HR days ANC (0.5 x 10^9/l)	PLT	Days	Median hospital stay (days)
1994	Liberti[69]	High-risk lymphomas	83	PSC	13	50 x 10^9/l	15.5	NR
			83	BM	18		27	
1994	Myers[57]	Metastatic breast cancer and BM metastases	5	PSC	14	20 x 10^9/l	41	NR
			14	PSC mobilized	13		18	
			8	PSC mobilized + G-CSF	11		10	
1994	Sheridan[171]	Lymphomas or acute lymphocytic leukemia	29	PSC mobilized with G-CSF		9-10	(range)	
						20 x 10^9/l	9-12	13
						50 x 10^9/l	11-37	
1994	Shpall[43]	High-risk breast cancer	7	BM	23	"Independence"	23	NR
			10	BM + G-CSF	13		16	
			8	BM + GM-CSF	18		18	
			12	BM + PSC + G-CSF	9		9	
			11	PSC + G-CSF	9		14	

Abbreviations: NR = not reported; PLT = platelet count; ANC = absolute neutrophil count; "Independence" = not requiring additional platelet transfusion.

Table 2. Comparison of median HR and hospital stay

Median HR (days)		Weighted average of median HR (days)		Median hospital stay (days)	Weighted average of median hospital stay (days)
ANC[a]	PLT[b]	ANC[a]	PLT[b]		
PSC 9-31	13.5-50	14.8	20.9	13-38.5	22.1
BM 13-33.5	13.5-48	20.1	29.1	25-38	31.5

[a]0.5 x 10^9/l.
[b]50 x 10^9/l.

than BM has almost halved the cost of an autograft for Hodgkin's disease (details were not provided).

The abstract reported that the addition of G-CSF-primed PSC to autologous marrow plus G-CSF resulted in significantly lower hospital charges than those incurred with the use of G-CSF plus autologous marrow without PSC (median $77,530 vs. $100,319).

Multiple HDCT trials with stem-cell support (albeit nonrandomized) have demonstrated conflicting outcomes in various tumor types, and the role of HDCT in such treatment continues to be undefined and is the subject of a number of ongoing clinical trials.[74,82,193,194] In addition, questions concerning issues of event-free survival and patient outcome using PSC (that appear to be at least comparable to that achieved using BM[69,195]) cannot be answered in the absence of prospective RCTs comparing APSCT vs. ABMT or with HDCT alone.[12,14,196]

The consensus panel of an international conference held in France in June 1993, to consider which diseases are or are not likely to benefit from HDCT trials with stem-cell rescue, suggested that adult acute myelocytic leukemia (AML) and acute lymphocytic leukemia (ALL), adult lymphomas, and adult solid tumors are diseases that should be evaluated in prospective RCTs to determine patient benefits in terms of risk and impact on survival.[180] This same panel also stated that, despite a good theoretic basis for HDCT plus stem-cell rescue, it has not been established as being superior to conventional therapy for any stage of any adult solid tumor.

A 1994 textbook on BMT stated that PSC may be used in patients in whom marrow harvest is not feasible, but questions of its preference to marrow and its cost benefit remain unanswered.[196]

In response to the *Federal Register* notice of this assessment[148] and the solicitation of information from organizations and institutions involved with stem-cell transplantation, the Office of Health Technology Assessment has received the following input.

Institutional Comments

The Cleveland Clinic Foundation (December 1993) stated that the indications for APSCT are essentially the same as those for ABMT. The advantages of using PSC are that their engraftment may be more rapid and may have less risk of contamination with tumor cells than autologous marrow. The use of PSC was also associated with a decreased incidence of infections and a decrease in the hospital length of stay compared with that for ABMT.

The Ohio Bone Marrow Transplantation Consortium (December 1993) provided a summary of their experience in the treatment of a variety of malignancies with APSCT during an 18-month period beginning in January 1992. A total of 99 patients were given transplants; the average hospital length of stay was 29 days and the average hospital charges were $94,220. This was compared with 111 patients treated with ABMT for whom the average hospital length of stay was 38 days and the average hospital charges were $127,692.

Disease indications for which autologous stem-cell transplantation is approved by the consortium are Hodgkin's and non-Hodgkin's lymphoma, CML, AML, ALL, neuroblastoma, breast cancer, testicular tumors, Wilm's tumor, Ewing's sarcoma, and rhabdomyosarcoma.

The Fox Chase Cancer Center (January 1994) members have commenced an APSCT program with studies involving ovarian cancer and non-small-cell lung cancer. As part of the Philadelphia Bone Marrow Transplantation Group, they will also participate in studies using PSC in breast cancer, and non-Hodgkin's lymphoma protocols.

The University of Nebraska Medical Center (January 1994) listed the following indications and contraindications for the use of PSC.

Indications:

1. Candidates for marrow ablative therapy and autologous transplant who have BM unsuitable for autografting because of too few cells, pelvic bone metastases, or marrow containing tumor cells not readily removable by purging techniques.
2. Candidates for marrow ablative therapy and an autologous transplant whose marrow cannot be harvested for technical reasons.
3. A less well-established (but potential) advantage of APSCT over ABMT may be that the patient is more likely to experience long-term, event-free survival. Postulated reasons for this include:
   a. PSC harvests are less likely to contain malignant cells than are BM harvests.
   b. The cytotoxicity of mononuclear and other cells collected with apheresis but not present in BM autografts may provide a direct therapeutic effect.
   c. Immune reconstitution (related to lymphocytes present in PSC harvests and absent from BM harvests) may allow for a more rapid immune surveillance and decrease the incidence of late infections.

Contraindications:

Candidates for HDCT who have evidence of circulating tumor cells on a routine blood smear or have too few progenitor cells in the circulation to provide a usable graft product.

The Washington University School of Medicine (January 1994) states that PSC were initially used in preference to BM in patients with hypocellular or fibrotic marrow due to prior therapy. Subsequent indications for APSCT included patients having tumor-involved marrow or metastatic lesions at the usual sites of harvests, or those unable to tolerate general or spinal anesthesia. In addition, PSC harvests engraft reliably, at a significantly faster rate than BM; usually contain fewer tumor cells than BM harvests; and may provide better immunologic reconstitution than BM.

Contraindications to the use of APSCT would be the inability to mobilize sufficient numbers of nucleated cells or the inability to tolerate apheresis.

There is a decreased cost of APSCT compared with ABMT, related to the shorter engraftment times, fewer days in hospital, and fewer infectious days. Costs of APSCT range from $60,000 to $120,000 on average around transplant centers in the United States.

Public Health Service Comments

The Food and Drug Administration (FDA; January 1994) stated that use of PSC is not currently a fully accepted therapy but is being actively explored as a substitute or comparable to use of BM in transplantation after myeloablative HDCT regimens. Other possible applications of PSC include support of, or faster, HR when BM is damaged but not ablated (myelosuppression), combined with BM to enhance engraftment after BM damage, use in patients in whom marrow is difficult to harvest because of fibrosis or other destructive processes, and use in patients whose marrow contains a heavy tumor burden not seen in peripheral blood. The FDA is currently collecting clinical data on the use of all hematopoietic stem cells with the view of developing standards and regulations for their clinical application.

The National Institutes of Health (December 1993) has provided the following information: Suggested advantages of PSC over the use of BM include easier collection and less contamination with tumor cells. Claims of more rapid HR using PSC have not been tested in a properly controlled trial, and limited studies comparing marrow with or without PSC have shown no significant difference. Disadvantages of using PSC include the monitoring of the timing of mobilization and harvesting and toxicities associated with cytokine mobilization.

Autologous peripheral stem-cell transplant may be used in situations in which ABMT is indicated. Diseases for which long-term, disease-free survival ("cure") is the goal commonly include refractory lymphomas, certain stages of breast cancer, AML in first relapse or later, neuroblastoma, and Wilm's tumor. For most other tumors, the use of autologous stem cells in HDCT regimens is more likely to be palliative, and its use outside of clinical trials is questionable. A possible exception is chronic myelogenous leukemia when an allogeneic donor is not available.

Summary and Conclusions

Circulating PSC can be obtained from a patient's blood for subsequent infusion after HDCT used to treat a variety of malignancies. This procedure, termed APSCT, is an effort to circumvent the morbidity and mortality associated with therapy-induced myelosuppression.

Initially, such supportive therapy was accomplished by stem cells obtained from BM. However, abundant clinical experience during the past 5 years has demonstrated that PSC may serve as a functionally equivalent alternative to BM in providing satisfactory HR. This is based, in part, on the perception that PSC harvests produce less morbidity than BM harvests, and that the purportedly more rapid HR will be as durable as that achieved using BM. Despite the absence of RCT proving its benefit, the use of APSCT has dramatically increased and already replaced BMT in many settings at many centers, and has generated predictions that it will soon replace BMT for most, if not all, clinical indications.

Suggested advantages offered by the use of PSC compared with BMT include accelerated HR, thereby reducing morbidity, mortality, and resources for supportive care; avoidance of general or spinal anesthesia for stem-cell harvests; use as an outpatient procedure; use in patients whose marrow is unsuitable for harvesting; and use in sequential HDCT regimens. In general, despite its widespread application, the therapeutic benefit of HDCT and PSC support has yet to be firmly established and is the subject of a number of ongoing clinical trials.

In the absence of appropriate RCTs, the current available data do not generate answers to questions concerning the efficacy and cost effectiveness of HDCT regimens, and additional studies are required to determine the optimum dosage and collection regimens for APSCT and whether disease-free survival rates are comparable to those achieved with ABMT. There continues to be a lack of standardization on the definition of a PSC autograft that will provide a satisfactory and timely HR.

In vitro PSC assays have not been defined, which makes for difficulties in comparing results from different institutions and promoting the diffusion of this technology beyond research centers. In the absence of negative or conflicting data, the existing evidence suggests that PSC can provide satisfactory HR. However, the rate of HR with PSC does not appear to be consistently different from that using BM. The clinical importance of HR continues to be secondary to the primary issue of the benefits of HDCT in terms of antitumor response, palliation, or survival.

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